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First Named Inventor

WASIELEWSKI, RAY C.

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3738

Examiner Name

SNOW, BRUCE EDWARD

Attorney Docket Number

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### ENCLOSURES (Check all that apply)

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Fee Transmittal Form

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Fee Attached

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Amendment/Reply

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After Final

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Affidavits/declaration(s)

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Extension of Time Request

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Express Abandonment Request

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Information Disclosure Statement

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Certified Copy of Priority Document(s)

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Petition

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REPLY BRIEF (7 PGS) W/ MATSUSUE REFERENCE (8 PGS)

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name

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Signature

Printed name

RYAN L. WILLIS

Date

11-17-2008

Reg. No.

48,787

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Sharon Shelton  
Sharon Shelton

**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:

Applicant : Wasielewski, Ray C.  
Filed : July 2, 2003  
Serial No. : 10/612,784  
Title : USE OF SNAP-ON SEMI-ANNULAR AUGMENTS TO  
INHIBIT MULTI-DIRECTIONAL INSTABILITY AFTER  
TOTAL HIP ARTHROPLASTY  
Docket No. : ORW01-GN004  
Examiner : Snow, Bruce Edward  
Art Unit : 3738  
Tech. Center : 3700

Hon. Commissioner for Patents  
Alexandria, VA 22313

Dear Sir:

**REPLY BRIEF**

The instant appeal is from the final rejection dated December 17, 2007. This Reply Brief is timely submitted in accordance with 37 C.F.R. § 41.41 and is in response to the Examiner's Answer mailed October 16, 2008.

**I. Introduction**

Applicant respectfully asserts that all of the rejected claims are properly supported by the specification and are allowable in view of the cited references. The Examiner's Answer does nothing but bolster Applicant's arguments. First, the Examiner clearly misunderstands what is encompassed by a "biologic material." Second, contrary to the Examiner's unsupported assertion, an agent promoting scar tissue formation does not mandate the carrier material (i.e., "augment material") itself form scar tissue. Third, objective evidence shows the claimed augment materials do not always form scar tissue, thereby refuting the Examiner's factually unsupported conclusions to the contrary. Fourth, the Examiner's Answer neglects to consider clear teachings away from the claimed invention, while also failing to cite any objective evidence supporting the Examiner's so-called "strong" position. Finally, even the Examiner's arguments implicitly support Applicant's position that the specification supports the recited limitations.

**II. Polyethylene is Not A Biologic Material, Nor is Polyethylene an Obvious Alternative to a Biologic Material. (Rejection 4)**

Paragraph [0025] of the specification defines a "biologic material" as a material being derived or synthesized from living organisms, cell, tissues, and/or their products that may or may not be bioresorbable. Despite this explicit definition, the Examiner continues ignore the bounds drawn by Applicant as his own lexicographer. For example, the Examiner asserts that "biologic" includes materials *not* bioresorbable, and cites polyethylene as an example.<sup>1</sup> But polyethylene is not a biologic material. And the fact that polyethylene would not be replaced by scar tissue is irrelevant because the claims would not read on a polyethylene augment. What is relevant, however, is the inability of the Examiner to cite a single reference disclosing a biologic material used as an augment material that did not form scar tissue. The absence of any such citation by the Examiner speaks for itself.

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<sup>1</sup> Examiner's Answer, p. 8 ("[I]t is the Examiner's position that it would have been obvious to one having ordinary skill in the art, ..., to have made the augment out of any material which is not bioresorbable, and therefore, would not be substantially replaced by scar tissue. Acetabular liner components are well known in the art being formed from non-bioresorbable materials such as polyethylene.").

**III. Augment Materials Not Transforming Into Scar Tissue, But That Contain An Agent To Promote The Formation Of Scar Tissue, Are Supported By The Specification. (Rejection 2)**

Claims 1, 24, 4-6, 14, 15, 27-32, and 37 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. When properly considered, it is objectively clear that the dispute centers around the Examiner's erroneous conflation of two distinct limitations concerning the "augment material." Contrary to the Examiner's assertions,<sup>2</sup> the specification supports claim limitations requiring: (1) an augment material that does not transform into scar tissue; and, (2) an augment material containing an agent to promote the formation of scar tissue. Throughout the prosecution of this application, the Examiner has refused to recognize the wholly separate and distinct nature of these two limitations, despite the specification making explicit this very distinction.

First, the specification unambiguously describes augment materials formulated so that each is absorbed and disappears without forming scar tissue.<sup>3</sup> Alternatively, the specification explains that augment materials "could also be formulated so as to be replaced by [scar] tissue."<sup>4</sup> The alternative nature of these examples is objectively clear to one skilled in the art reading the specification. In addition, regardless of the nature of the augment material to form scar tissue or not, the augment material can be supplemented with a scar tissue promoter.

The specification makes clear that augment materials may be optionally supplemented with one or more "agents," some of which promote the formation of scar tissue.<sup>5</sup> Simply including an agent to promote scar tissue formation does not mandate a carrier material, in this case the augment material, that transforms into scar tissue. While a scar tissue promoting agent

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<sup>2</sup> Examiner's Answer, page 3 ("The specification does not support a material that does not transform into scar tissue but contains an agent to promote scar tissue.").

<sup>3</sup> Application as filed, paragraph [0040] ("augments 26 could be formulated to be absorbed over a relatively short period (i.e., several weeks or months)").

<sup>4</sup> Application as filed, paragraph [0040] ("augments 26 could be formulated to be absorbed over a relatively short period (i.e., several weeks or months) and could also be formulated so as to be replaced by tissue (such as scar-tissue)" (emphasis added)).

<sup>5</sup> Application as filed, paragraph [0044] ("It is within the scope of the present invention to 'load' (disburse, coat, impregnate, etc.) the biologic and/or biologically reabsorbable materials comprising the snap-on augments 26 and the male fasteners 28 with agents that could hasten or assist in tissue development, assist in clotting, and/or fight infection." (emphasis added)).

*could* be loaded into an augment material that *does* transform into scar tissue, the specification also supports a combination of a scar tissue promoting agent with an augment material that *does not* transform into scar tissue.<sup>6</sup> Yet the Examiner has provided no factual basis for reading out such a combination from the specification nor for obfuscating the separate nature of the foregoing limitations (augment material properties vs. promoting agent properties). In fact, the only reasoning articulated by the Examiner to support his position is factually inaccurate.

Notably, the Examiner baldly and inaccurately asserts, “One skilled in the art would not read the list of augment materials disclosed in the originally filed application and conclude the augments are ‘formulated not to transform into scar tissue.’”<sup>7</sup> This totally unsupported, conclusory allegation, was made for the first time in the Examiner’s answer and is factually incorrect. At least one formulation of PLLA, one of the claimed augment materials recited in originally filed claim 5, has been observed and discussed in published literature to be “absorbed completely without any scar tissue formation”<sup>8</sup> when implanted into a mammalian body. In other words, “[o]ne skilled in the art would [] read the list of augment materials disclosed in the originally filed application and conclude [that at least some of] the augments are ‘formulated not to transform into scar tissue.’” Even the Examiner implicitly agrees that the specification supports such a limitation.

Applicant’s argument that the claimed subject matter is supported by the specification is bolstered by the reasoning underlying the Examiner’s Answer statement, “the specification teaches ‘formulated to be replaced by’ and not ‘transform’ as claimed which is different in scope.”<sup>9</sup> The premise of the Examiner’s assertion is “formulated to be replaced by” does not encompass “transform;” otherwise, the Examiner’s argument would make no sense. But the only

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<sup>6</sup> Application as filed, paragraph [0044] (“It is within the scope of the present invention to ‘load’ (disburse, coat, impregnate, etc.) the biologic and/or biologically reabsorbable materials comprising the snap-on augments 26 and the male fasteners 28 with agents that could hasten or assist in tissue development, assist in clotting, and/or fight infection.” (emphasis added)).

<sup>7</sup> Examiner’s Answer, page 7.

<sup>8</sup> See, e.g., Matsusue et al. “Tissue Reaction of Bioabsorbable Ultra High Strength Poly (L-Lactide) Rod,” Clinical Orthopaedics and Related Research, No. 317, pp. 246-253, August 1995. A copy of this reference is attached, and a this reference is disclosed in a supplemental Information Disclosure Statement. This reference is newly submitted to directly refute the factually incorrect assertion made the Examiner for the first time in his Examiner’s Answer, despite having the opportunity of the Examiner to make this same assertion in four prior Office actions.

<sup>9</sup> Examiner’s Answer, page 7.

construction of “formulated to be replaced by” that might be argued not to encompass “transform” is the circumstance where the augment material dissolves and scar tissue forms in its place (i.e., scar tissue formation occurs, but not by using the augment material itself). Yet this construction is precisely what the Examiner argues is unsupported by the specification. Accordingly, if the Board agrees with the Examiner that “formulated to be replaced by” does not encompass “transform,” such a conclusion cannot be consistent with a finding that the specification does not support a disclosure of an augment material not transforming into scar tissue. In summary, the specification discloses augment materials formulated not to transform into scar tissue that may be supplemented with an agent to promote the formulation of scar tissue. As a result, the pending claims do not include any new matter. Applicant respectfully requests reversal of the § 112, second paragraph, rejections.

**IV. Claims 1, 24, 4-6, 14, 15, 27-32, and 37 Are Non-Obvious Over Klüber. (Rejection 4)**

Claims 1, 24, 4-6, 14, 15, 27-32, and 37 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Klüber (DE 19716051). However, independent claims 1 and 27 require, and Klüber does not disclose, forming the augment of a material that “is formulated not to transform into scar tissue.” Klüber explicitly teaches that “[t]he resorbable luxation securing ring . . . is transformed into yielding connective tissue,”<sup>10</sup> “the ring and attaching screws are transformed into flexible native connecting tissue,”<sup>11</sup> and “transformation into flexible native connecting tissue also result[s] in long-term protection against dislocations . . . .”<sup>12</sup> Klüber only teaches a ring material transforming into scar tissue. If anything, Klüber teaches away from the claimed invention where scar tissue transformation from the augment material does not occur. Accordingly, it is illogical to conclude that Klüber, which touts the advantages of scar tissue formation, somehow renders obvious claims 1 and 27 that require materials formulated *not* to transform into scar tissue.

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<sup>10</sup> Klüber, first page, section (57), first paragraph.

<sup>11</sup> Klüber, Description section, third paragraph.

<sup>12</sup> Klüber, Description section, sixth paragraph.

**Reply Brief**  
**Serial No. 10/612,784**  
**Docket No. ORW01-GN004**

In addition, the Examiner explicitly admits that “Kuber [sic] fails to teach the augment material is supplemented with at least one of an agent to promote the formation of scar tissue, a clotting agent, and an antibacterial agent,”<sup>13</sup> which is required by claim 1. Nevertheless, the Examiner baldly asserts that such a formulation would be obvious. “It is the Examiner’s strong position that applicant claiming an antibacterial agent, for example, on a bone prosthesis to prevent infection is not a novel, patentable limitation.” Yet the Examiner has not bothered to cite a single piece of objective evidence tending to support his position now or in the previous Office actions. And the Examiner had four Office actions to so, but declined each time. Even the Examiner’s manifestly erroneous reference to a “novel, patentable limitation” reflects a complete misunderstanding of how one correctly assesses patentability.

Contrary to the Examiner’s tact, there is no “point of novelty” test for assessing patentability under 35 U.S.C. § 103. Rather, it is the claim as a whole that is assessed. Specifically, the correct question is whether the claimed invention, as a whole and considering all of the claim limitations, would be obvious. And the answer to this question is clearly no. Notably, the Examiner asserts, “It is the Examiner [sic] belief that all materials listed in claim 5 which depend from claim 1 meet the limitation of claim 19 and would be substantially replaced by scar tissue.”<sup>14</sup> Again, this argument was presented by the Examiner for the first time in the Examiner’s Answer, despite having four Office actions to make such an assertion. Nevertheless, the Examiner’s assertion is totally irrelevant because claim 19 did not depend from claim 5. Rather, claim 19 depended from claim 1. Accordingly, the Examiner’s conclusion is completely unfounded on a claim dependency basis. Moreover, as discussed above, Applicant has produced objective evidence that at least PLLA, which is recited in claim 5, has been observed not to form scar tissue in certain formulations.

Claim 27 also recites that “the semiannular augment includes at least one integrated fastener,” and the Examiner asserts that Klüber’s screw is an integrated fastener. The Examiner’s position is blatantly incorrect. Klüber explicitly states, “The luxation retaining ring

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<sup>13</sup> Examiner’s Answer, page 5.

<sup>14</sup> Examiner’s Answer, page 8.

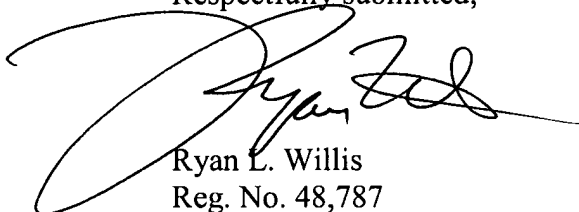
has corresponding prepared bored holes (G) to receive the screws.”<sup>15</sup> Screws that are “received” in “bored holes” in the luxation ring are not integrated with the luxation ring. Again, the Examiner’s rejection is factually unsupported.

For at least these reasons, it is apparent that the Examiner has not properly considered all of the claim limitations. Applicant respectfully asserts that independent claims 1 and 27, and the claims depending therefrom, are patentable over the references cited and, accordingly, reversal of the § 103 rejections is respectfully requested.

**V. Withdrawal of Rejections**

Applicant acknowledges the withdrawal of the rejection of claims 1, 2, 4-6, 14, 15, 27-32, 37-39, and 109 under 35 U.S.C. § 112, second paragraph (Rejection 1), and the rejection of claims 1, 2, 4-6, 14, 15, 27-32, 37, and 109 under 35 U.S.C. § 102(b) as allegedly anticipated by Klüber (Rejection 3).

Respectfully submitted,



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<sup>15</sup> Klüber, first page, section (57), second paragraph.

# Tissue Reaction of Bioabsorbable Ultra High Strength Poly (L-Lactide) Rod

*A Long-Term Study in Rabbits*

*Yoshitaka Matsusue, MD, PhD\*; Shinya Hanafusa, MD\*;  
Takao Yamamuro, MD, PhD\*; Yasuo Shikinami, PhD\*\*;  
and Yoshito Ikada, PhD\*\**

Bioabsorbable ultra high strength poly (L-lactide) rods, which were developed for internal fixation of fractures, were fabricated using a drawing technique. These rods were implanted in the subcutaneous tissue and in the medullary cavity of rabbits to investigate tissue reactions to poly (L-lactide) and to study their degradation process. After 18 months, histiocytes were found, and their phagocytic activity continued for as long as 42 months, with maximum activity observed between 24 and 36 months after implantation. At 62 months after intramedullary implantation, the materials had been absorbed almost completely and were replaced by bone marrow cells, with only a small amount of residual tissue reaction. At 69 months after subcutaneous implantation, the materials had been absorbed completely without any scar formation. During degradation, no foreign body giant cells were found and osteolytic expansion caused by liquid degradable materials was not seen.

Absorbable fracture fixation devices made of biodegradable synthetic polymers have been used as an alternative method of internal fixation for human fractures, particularly peri- or intraarticular fractures.<sup>3,16,22,27</sup> To date, the overall results have been favorable, but in approximately 8% of the patients treated with self-reinforced polyglycolide rods, a tissue reaction develops at the implantation site. These reactions range from a small discharging sinus to an intense reaction requiring repeated surgical drainage procedures.<sup>3-8</sup>

In animal studies, implants made of polyglycolide, lactide-glycolide copolymers, or polydioxanone produced a foreign body reaction in bone.<sup>10,12,15,17,29,31</sup> Böstman et al,<sup>7</sup> at 36 weeks after implantation in rabbit femora, showed degradation and tissue replacement of an absorbable polyglycolide screw, accompanied by engulfment of the birefringent polymeric particles by phagocytic cells and marked proliferation of loose connective tissue within the implant cavity. Vasenius et al<sup>30</sup> also found that a fluid accumulation expanding into the bone marrow was detected 12 weeks after implantation in a similar animal model.

Tissue reactions to poly (L-lactide) have been described by several authors since 1966.<sup>2,11,13,20,24,26,31</sup> Recently, Bergsma et al<sup>1</sup> reported the results of long-term implantation in patients successfully treated with zygomatic fractures using poly (L-lactide)

plates and screws.<sup>1</sup> Typically, 6 of 10 patients for evaluation of swelling site because of a nonreaction to the degradable material. In another study, matory foreign body reaction) implants were re long-term animal study (L-lactide) implants for bones has been reported.

The authors have a strength poly (L-lactide) internal fixation of fracture technique.<sup>25,26</sup> The initial poly (L-lactide) rod (240 MPa) is the highest infomed poly (L-lactide) investigations of

The authors have studied in vivo behaviors of these rods and evaluated the weeks after intramedullary. The present study has second part of histology these ultra high strength plants. The aim of this the long-term results of these materials.

## MATERIALS AND METHODS

Synthesis of the L-lactide opening polymerization is detail elsewhere.<sup>13</sup> The molecular weight ( $\bar{M}_n$ ) of poly (L-lactide) was 10<sup>5</sup> daltons. Poly (L-lactide) was drawn in a mechanical die at 200°C, which was described previously.<sup>26</sup> The resulting  $\bar{M}_n$  of the poly (L-lactide) was 10<sup>5</sup>. Rods with a diameter of 5 cm were modeled by the in vivo histologic study and bending modulus of were measured by the 3-point bending test according to Japanese Industrial Standard JIS Z 2203 (Autograph SD-100-C, Japan). The bending strength

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plates and screws.<sup>1</sup> Three years postoperatively, 6 of 10 patients required reoperation for evaluation of swelling at the implantation site because of a nonspecific foreign body reaction to the degraded poly (L-lactide) material. In another study, no signs of inflammatory foreign body reaction to poly (L-lactide) implants were reported.<sup>22</sup> No detailed long-term animal study of high strength poly (L-lactide) implants for fixation of fractured bones has been reported.

The authors have developed ultra high strength poly (L-lactide) rods and screws for internal fixation of fractures using a drawing technique.<sup>25,26</sup> The initial bending strength of the poly (L-lactide) rods used in this study (240 MPa) is the highest reported for nonreinforced poly (L-lactide) rods used in detailed investigations of degradation.<sup>14,21,23,26</sup>

The authors have studied the *in vitro* and *in vivo* behaviors of these poly (L-lactide) rods and evaluated the tissue reaction for 78 weeks after intramedullary implantation.<sup>26</sup> The present study has been designed as the second part of histologic investigations of these ultra high strength poly (L-lactide) implants. The aim of this study was to clarify the long-term results of tissue reaction of these materials.

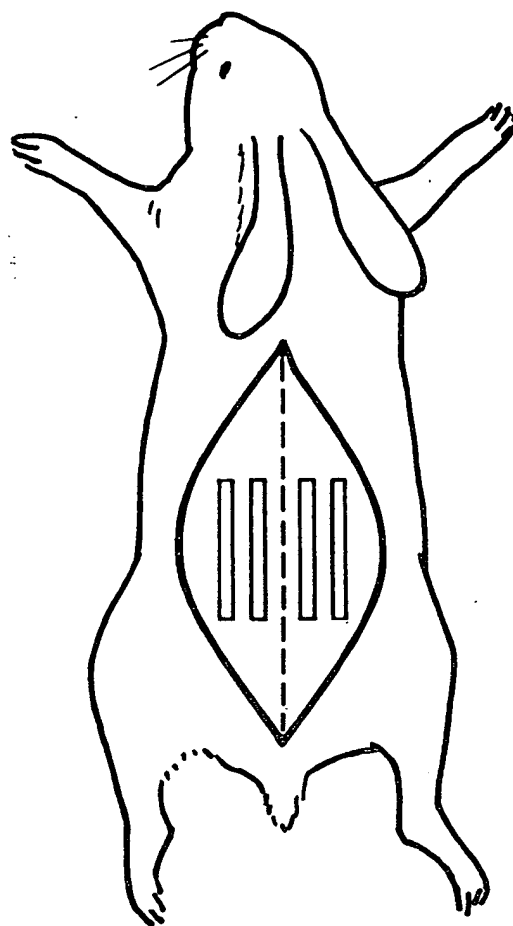
## MATERIALS AND METHODS

Synthesis of the L-lactic acid dimer and its ring opening polymerization have been described in detail elsewhere.<sup>18</sup> The viscosity-average molecular weight ( $\bar{M}_v$ ) of poly (L-lactide) was  $4 \times 10^5$  daltons. Poly (L-lactide) was extruded into cylindrical rods at 200° C, which were then uniaxially drawn in a mechanical direction at 100° C as described previously.<sup>26</sup> The draw ratio was 2.5:1. The resulting  $\bar{M}_v$  of the poly (L-lactide) was  $2.2 \times 10^5$ . Rods with a diameter of 3.2 mm and a length of 5 cm were modeled by a machining process for the *in vivo* histologic study. The bending strength and bending modulus of poly (L-lactide) rods were measured by the 3-point bending method according to Japanese Industrial Standard using an Autograph SD-100-C (Shimadzu Co, Kyoto, Japan). The bending strength and modulus of

these rods were 240 MPa and 13 GPa, respectively. All rods used in this study were sterilized with ethylene oxide at 40° C for 5 hours without H<sub>2</sub>O.

Japanese male rabbits weighing between 3.0 and 3.5 kg were used in this study. Thirty-five rabbits were anesthetized by intravenous injection of 0.5 ml/kg of Nembutal (Taito Pfizer, Tokyo, Japan). After all surgical procedures, the rabbits were kept in cages and maintained with regular laboratory diet. In the first group (Group A) of 5 rabbits, 4 poly (L-lactide) rods were implanted in the dorsal subcutaneous tissue of each rabbit (Fig 1). In the second group (Group B), rods were implanted intramedullary into both femora of 30 rabbits. A medial parapatellar incision was made, and the patella was laterally dislocated. Subsequently, a longitudinal drill channel 3.2 mm in diameter was made through the intercondylar area of the femoral condyle. After washing out the drill hole with 20 ml of saline, the rod was inserted with a pusher and was fixed snugly into the femoral canal (Fig 2). The capsule and incision were closed with 4-0 braided nylon sutures.

After 20 rabbits in Group B had been used in a previous short-term histologic study<sup>26</sup> after intramedullary implantation, the remaining 15 were used in this long-term histologic study. A followup period of 48 months was planned initially for all rabbits, but most of them died of old age or of unknown causes before this time. The longest period of observation was 69 months postoperatively. Two rabbits in Group A were sacrificed by Nembutal overdose at 24 and 48 months after implantation. The other rabbits died of unknown causes at different times after the second year of followup (Fig 3). Samples taken from these rabbits were studied histologically. In Group A, after determining the localization, the rods and surrounding soft tissue in the subcutis were excised en bloc with scalpel and scissors at 18, 24, 48, and 69 months after surgery. In Group B, the distal portions of both femora of each rabbit, free of the soft tissue, were removed at 18, 24, 31, 33, 34, 41, 42, and 62 months after rod implantation. The distal 2 cm of the removed femur was fixed with phosphate-buffered formalin solution, decalcified, and embedded with paraffin for histologic investigations. Six 5- $\mu$ m-thick sections were cut from each specimen and were stained with hematoxylin and eosin.



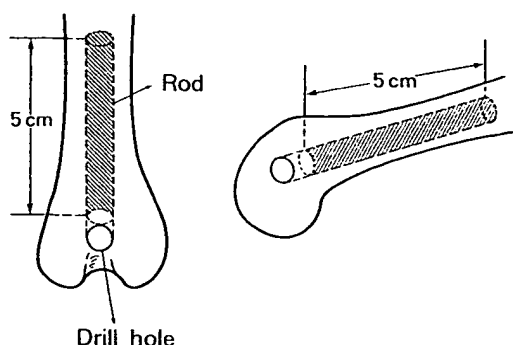
**Fig 1.** Schematic representation of subcutaneous implantation of the poly (L-lactide) rods. Four rods with a diameter of 3.2 mm and a length of 5 cm were implanted in the subcutaneous tissue of the back of each rabbit.

## RESULTS

### Macroscopic Findings

All animals recovered well from their operations, and there were no signs of infection or inflammatory reaction.

**Group A:** By 18 months all rods in 2 rabbits had become white and porous. They were very brittle and surrounded by a dense fibrous capsule, so it was impossible to remove most of them in 1 piece. At 24 months



**Fig 2.** Schematic representation of intramedullary implantation of the rods. A 5-cm rod was inserted into the femoral canal of both knees of each rabbit. A distal 2 cm of each femur, free of the soft tissue, was used for histologic study.

after implantation, the findings were similar to those at 18 months. At 48 months after subcutaneous implantation, the rod could not be detected, and only a small amount of scar tissue with proliferation of small vessels was found on the fascia of the back muscle. At 69 months after subcutaneous implantation, the rods had been absorbed completely without any evidence of scar formation.

**Group B:** There were no complications during or after the operations, such as patellar dislocation or joint stiffness. By 24 months after intramedullary implantation,

Group							
Group A	●	●	○	○	●	●	
Follow-up Periods (Months)	12	24	36	48	60	72	
Group B	●	●	●	●	●	●	

**Fig 3.** Schematic representation of the followup periods of the rabbits used in this study. Group A: subcutaneously implanted group; Group B: intramedullary implanted group. (○ = rabbit sacrificed by Nembutal overdose; ● = rabbit died spontaneously.)



**Fig 4A-B.** (A) Photomicrograph of a section of poly (L-lactide) rod 48 months after subcutaneous implantation at a low power. The poly (L-lactide) rod is absorbed and cannot be detected. A thin layer of the residual histiocytes (arrows) is found along the loose connective tissue. (Stain, hematoxylin and eosin; original magnification,  $\times 100$ ; bar,  $50\text{ }\mu\text{m}$ .) (B) Photomicrograph of the same section at a high power. (Stain, hematoxylin and eosin; original magnification,  $\times 400$ ; bar,  $10\text{ }\mu\text{m}$ .)

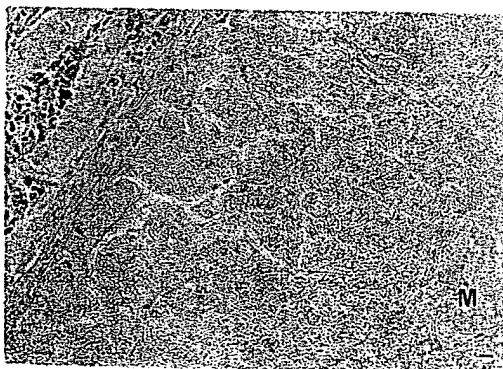
the space where the rod was implanted in the medullary canal could be identified from the bony or fibrous tissue surrounding the degraded rod because its color was slightly brighter than that of the surrounding bone marrow. Between 24 and 42 months after implantation, the findings were similar to those of 24 months. At 62 months after intramedullary implantation, the rod could not be identified and the space where it was implanted seemed to have been replaced by bone marrow.

### Histologic Findings

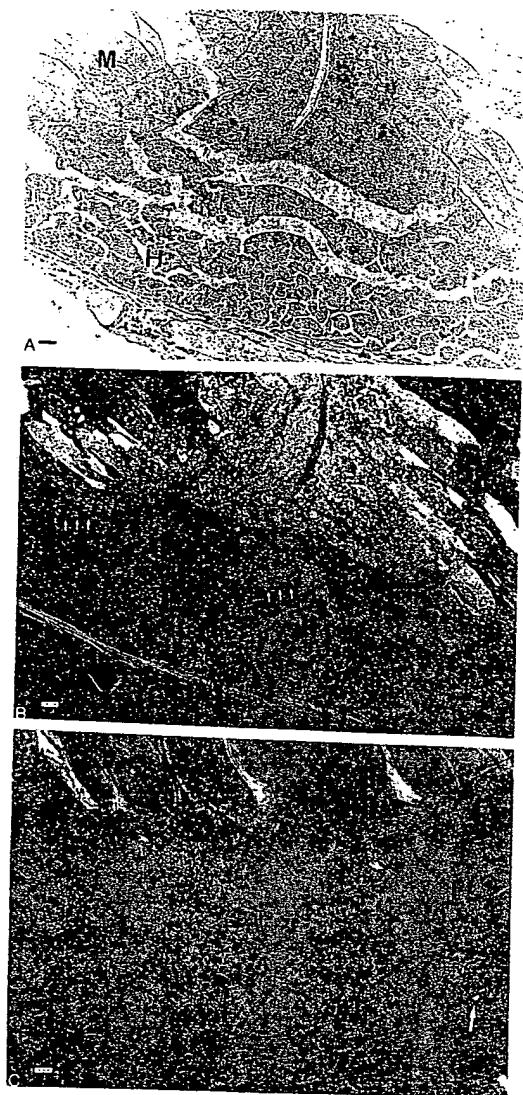
**Group A:** At 18 months after implantation a fibrous tissue layer approximately  $200\text{-}\mu\text{m}$

thick was observed surrounding the rods. Some of this fibrous tissue invaded the cracks in the material. A layer of histiocytes 1- to 2-cells thick was found in the cracks. By 24 months, a layer of histiocytes 5- to 6-cells thick was detected between and surrounding the rods, and the fibrous tissue layer was thicker than at 18 months. At 48 months after implantation, the degraded polymer could not be detected, no giant cells were present, and only a layer of histiocytes several-cells thick was found (Fig 4). At 69 months, the rods had been absorbed completely and there was no evidence of the degraded polymer. The tissue taken from the fascia where the materials had been implanted showed normal fibrocollagenous tissue without any scar formation.

**Group B:** At 18 months after implantation, the bony encapsulation became thinner and numerous small pieces of the degraded polymer were found. Only a small amount of fibrous tissue invaded the degraded rod. A layer of histiocytes 2- to 3-cells thick was found between the rod and the bony encapsulation. At 24 months, numerous histiocytes appeared in the periphery of the degraded



**Fig 5.** Photomicrograph of a section of poly (L-lactide) rod 33 months after intramedullary implantation. Numerous histiocytes that are phagocytizing the small pieces (approximately  $<2\text{-}3\text{ }\mu\text{m}$ ) of the degraded polymer are found in the periphery of the material (M). A thin layer of fibrous tissue surrounds the histiocytes. (Stain, hematoxylin and eosin; original magnification,  $\times 400$ ; bar,  $10\text{ }\mu\text{m}$ .)



**Fig 6A–C.** (A) Photomicrograph of a section of poly (L-lactide) rod 41 months after intramedullary implantation. A layer of histiocytes 5- to 6-cells thick (H) were found in the periphery of the rod. The degraded materials (M) were still present in the center. (Stain, hematoxylin and eosin; original magnification,  $\times 200$ ; bar, 25  $\mu\text{m}$ .) (B) Polarized light photomicrograph of the same section at a low power. The birefringent polymeric particles (arrows) are detected mainly in the layer between the material-rich layer and the histiocyte-rich layer. (Stain, hematoxylin and eosin; original magnification,  $\times 200$ ; bar, 25  $\mu\text{m}$ .) (C) Polarized light photomicrograph of the same section at a high power. Few birefringent particles (arrow) were detected within phagocytic cells (histiocytes). (Stain, hematoxylin and eosin; original magnification,  $\times 400$ ; bar, 10  $\mu\text{m}$ .)

rods, but most of the polymer was present in the central area. A small amount of poly (L-lactide) particles was detected between these histiocytes. Foreign body giant cells were not present. Between 24 and 42 months, the histologic findings were very similar to those observed at 24 months (Fig 5). The particles of degraded polymer were still present in the central area of the rod that had not been replaced by bone and tissue. Numerous histiocytes that were phagocytizing the small

pieces (approximately  $<2$  to  $3 \mu\text{m}$ ) of the degraded polymer were found in the periphery of the rod (Fig 6). The birefringent polymeric particles were detected under polarized light in the layer between the material rich layer and the histiocyte rich layer (Fig 6). However, few birefringent particles were detected within phagocytic cells (histiocytes). At 62 months, the implanted materials had been absorbed almost completely and replaced by bone marrow cells. No birefrin-

gent polymeric material could be seen. A small amount of residual histiocytes were found in the center where the rod was implanted (Fig 7).

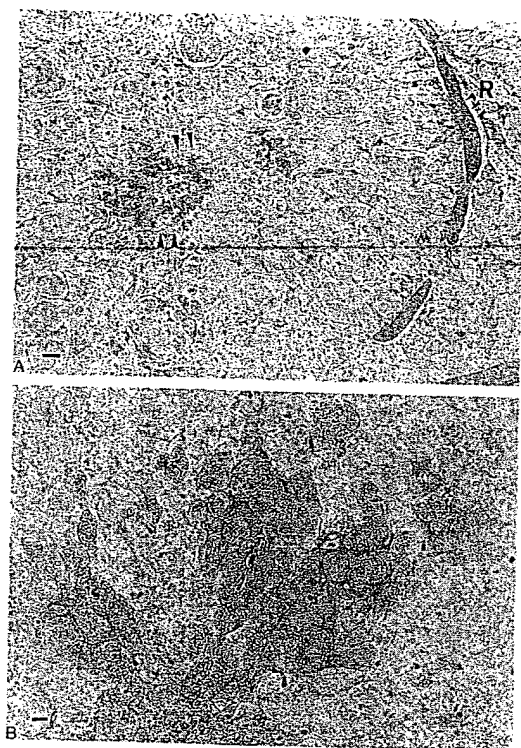
## DISCUSSION

Earlier studies by the authors showed rapid decrease of the viscosity-average molecular weight of poly (L-lactide) in the first 2 months and complete loss of mechanical

strength within 6 months after implantation.<sup>26</sup> Therefore, the authors initially considered that the poly (L-lactide) implants would be absorbed within a few years. Actually, it took much longer for the poly (L-lactide) implants to be absorbed completely, and the absorption process generally extends beyond the average span of a laboratory rabbit life. The implants and surrounding tissue were examined as the rabbits died naturally; thus few of them were examined at each time point. Only 2 rabbits survived for 5 years, and complete absorption of poly (L-lactide) had occurred. This is the first report of complete absorption of the ultra high strength poly (L-lactide) implants.

According to the authors' previous studies, the degradation pattern of poly (L-lactide) is summarized as follows.<sup>25,26</sup> The viscosity-average molecular weight decreases first during 3 months after implantation and the histologic findings show a reactive bone formation interposed with a layer of fibrous tissue. Three months after implantation, the mechanical strength decreases and then material weight decreases before the development of phagocytosis by histiocytes at 18 months after intramedullary implantation. By 52 weeks, only a small number of histiocytes are found in the fibrous tissue layer between the material and the reactive bony encapsulation.

Phagocytosis by histiocytes was the main characteristic of degradation of poly (L-lactide). These histiocytes contained numerous small particles, which are probably the final degradation products of poly (L-lactide) even though they were scarcely birefringent under polarized light. A moderate amount of birefringent particles was present in the more central area. Böstman et al<sup>5,6-8</sup> reported that birefringent fragments of the degrading self-reinforced polyglycolide implants were surrounded by masses of neutrophilic polymorphonuclear leukocytes and multinucleated foreign body giant cells in animal studies and clinical cases. In this study, however, there were no giant cells phagocytizing relatively large particles (range, 10–15  $\mu\text{m}$ ) of the degraded polymers as is the case with self-reinforced polyglycolide im-



**Fig 7A–B.** (A) Photomicrograph of a section of poly (L-lactide) rod 62 months after intramedullary implantation at a low power. The material is almost completely absorbed, and a small focus of residual tissue reaction (arrows) is found in the center where the material was implanted. A residual bony encapsulation (R) is found in the periphery. (Stain, hematoxylin and eosin; original magnification,  $\times 40$ ; bar, 100  $\mu\text{m}$ .) (B) Photomicrograph of the same section at a high power. Residual tissue reaction composed of histiocytes were found. (Stain, hematoxylin and eosin; original magnification,  $\times 400$ ; bar, 10  $\mu\text{m}$ )

plants.<sup>7</sup> Probably, the larger particles produced as a result of degradation of the self reinforced or highly oriented biodegradable polymers may stimulate macrophages and evoke a foreign body giant cell reaction during the final stage.<sup>7</sup> Because this poly (L-lactide) implant does not contain fibrils in its structure, and its crystallinity is relatively low, the smaller particles from poly (L-lactide) generate phagocytosis by histiocytes (macrophages) that are mononuclear. The appearance of phagocytic cells (histiocytes) in this study represents a mild and chronic foreign body tissue reaction that could be detected only by histologic investigations. This finding is in agreement with previous reports.<sup>2,3,4</sup> In addition, the scattered fluid accumulation (osteolytic expansion) that was reported for self-reinforced polyglycolide osteosynthesis implants<sup>30</sup> was not apparent.

Tissue reaction of the poly (L-lactide) implanted in the subcutis was almost similar to that of the intramedullary implanted poly (L-lactide) except for bony encapsulation. At 48 months after implantation, no giant cells were found and only a thin layer of histiocytes was found. These findings illustrate the final stage of absorption of poly (L-lactide). The poly (L-lactide) implants in this study, however, may produce a clinically manifest tissue reaction if they are placed superficially, such as in the subcutis, or in locations where the fractures are unstable and much stress is transmitted to the implants. Bergsma et al<sup>1</sup> probably noted effusion because they used subcutaneous implantation of a large volume of high initial molecular weight ( $1 \times 10^6$ ) polymer in a small bone (zygoma). This complication may result because a big bulk of poly (L-lactide) fragments may exceed the clearing capacity of the surrounding tissue.<sup>1</sup>

With respect to the biocompatibility of biodegradable polymers, in a rabbit cornea assay<sup>19</sup> vascular invasion and other inflammatory responses were much less observed in poly (L-lactide) relative to other biodegradable polymers. Furthermore, it was

apparent that the same concentration of glycolic acid, a stronger acid than lactic acid, caused more inflammation. van Sliedregt et al,<sup>28</sup> through an intraperitoneal injection model in mice, found that the inflammatory response observed in the peritoneal cavity is related to the type of material injected and probably to the form and the size of the individual particles. These results are in accordance with those of the authors' long-term study on poly (L-lactide).

The poly (L-lactide) implants in this study seem to be absorbed between 4 and 5 years after implantation. This slow degradation of poly (L-lactide) is an apparent drawback to its use in surgical implantation because most fractures for which poly (L-lactide) implants are used heal within a couple of months. Nevertheless, the long degradation time of poly (L-lactide) does not disturb the fracture healing because the stress-protection effect is rapidly lost.<sup>2</sup> The slow degradation of poly (L-lactide) probably reduces the inflammatory responses that are common with polyglycolide.

The complete absorption of the ultra high strength poly (L-lactide) implant has been shown in this study, and the tissue reaction composed of mononuclear cells (histiocytes) was characteristic of the degradation process of poly (L-lactide). Devices made of poly (L-lactide), such as nails, rods, and various types of screws, are being used in the orthopaedic field; to date, no obvious tissue reaction such as late aseptic effusion has occurred.

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